REMARKS

Claims 53, 55-58 and 60-63 are currently pending in this application. In view of the following remarks, Applicants submit that all the claims are in condition for allowance.

Claims 53, 55-58 and 60-63 stand rejected under 35 U.S.C. 103(a) for purported obviousness in view of U.S. Patent No. 5,648,059 ("the '059 patent"), U.S. Patent No. 5,843,894 ("the '894 patent") and Hammond et al. (Br. J. Cancer, 1993, 67:1437-1439; "Hammond"). The Examiner asserts that the '059 patent teaches L-lysine, arginine and ornithine as useful for inhibiting the retention and reabsorption of therapeutic immunoconjugates, such as antibodies and monoclonal antibodies. In particular, the '059 patent discloses decreased protein uptake by a rat kidney with a 10 mg dosage of lysine. The Examiner further asserts that the '894 patent teaches an effective dosage of lysine and polylysine of 2-35 g/L and 10-25 g/L, respectively, for reducing uptake of antibody fragments. Finally, the Examiner asserts that Hammond teaches that 4.93 g/L of lysine and 17.6 g/L of arginine is useful in blocking renal tubular uptake of somatostatin. The Examiner states that the references do not expressly teach the claimed dosage amounts of lysine and arginine of the present invention.

With respect to the '059 patent, Applicants respectfully disagree that it teaches or suggests, alone or in combination, the key inventive feature of the present invention, which is the co-administration of low dosage amounts of lysine and arginine. Rather, the '059 patent discloses administering an effective amount of a non-target reduction moiety, in which the preferred non-target reduction moiety is lysine and functional constituents or derivatives thereof. Although other moieties are disclosed as possible non-target reduction moieties, nowhere does the '059 patent teach co-administration of lysine with the other non-target reduction moieties. Furthermore, the disclosure of other non-target reduction moieties is provided in a list that happens to include "ornithine, arginine, epsilon amino caproic acid, cyclocaprone and the like." (Column 5, lines 18-19). More importantly, the '059 patent expressly states that "lysine is the preferred non-target reduction moiety for use in the present invention." (Column 5, lines 20-21), and thus effectively teaches away from combining lysine with other amino acids generally, or arginine in particular.

Applicants submit that such a general disclosure of a list of agents, one of which happens to be arginine, does not teach or suggest the co-administration of lysine and arginine in specific low dosage amounts which results in the new and unexpected synergistic effects of the claimed invention.

With respect to the '894 patent, it teaches a method of reducing kidney uptake of antibody fragment conjugates by solely administering lysine, either alone or as a mixture of at least two of D-lysine, poly-D-lysine or poly-L-lysine. Nowhere does the '894 patent teach or suggest the co-administration of specific low dosage amounts of lysine and arginine. Furthermore, as discussed in the present application (on page 3, line 13 to page 4, line 3), there are several disadvantages to administering lysine alone. In particular, Applicants have demonstrated that L-lysine administration in humans in an effective total dose of 75 grams may cause severe hyperkalemia which may result in acute and life-threatening cardiotoxicity.

Finally, with respect to Hammond, Applicants respectfully disagree that it teaches the co-administration of lysine and arginine. The Examiner directs Applicants' attention to page 1437, column 2, the Materials and Methods section, wherein it is stated that "the amino acid preparation administered was Synthamin 14 without electrolytes, containing 4.93 g/l lysine and 17.6 g/l arginine and with a tonicity of 880 mosm/l..." Hammond, therefore, actually teaches the administration of Synthamin 14, which is a commercially available cocktail of various amino acids (discussed in the present application on page 2, second paragraph), which happens to contain lysine and arginine along with thirteen other amino acids. As stated in the present application, such amino acid cocktails usually comprise a total amount of about 100 grams or more of various amino acids which, as stated above, may cause severe hyperkalemia and which may result in acute and life-threatening cardiotoxicity.

The amino acid composition of Synthamin 14 disclosed in Hammond is known from the literature and contains the following amino acids:

Substance	**Quantity (g/L)**	**Total Quantity in 2 L**
Glycine	8.80	17.60
L-arginine	17.60	35.20
L-histidine	4.08	8.16
L-methionine	3.40	6.80
L-proline	5.78	11.56
L-threonine	3.57	7.14
L-valine	4.93	9.86
L-serine	4.25	8.50
L-alanine	9.80	19.60
L-isoleucine	5.10	10.20
L-leucine	6.20	12.40
L-lysine	4.93	9.86
L-phenylalanine	4.75	9.50
L-tryptophan	1.53	3.06
L-tyrosine	0.34	0.68
Total amino acids:	85.06 g/L	170.12 grams

As shown above, the total quantity of amino acids administered and the osmolarity of the amino acids are significantly higher than another commercially available cocktail, Aminosteril N, which composition is provided on page 10, line 15 to page 11, line 4 of the present application, and which effects in patients after administration is described in Examples 4 and 5 of the present application. In particular, the total quantity of amino acids in Aminosteril N is 83.01 g/L (compared to 85.06 g/L in Synthamin 14); the total quantity of amino acids in a 2 L infusion is 166.03 grams (compared to 170.12 grams in Synthamin 14); and the osmolarity is 770 mosm/L (compared to 880 mosm/L in Synthamin 14).

The side-effects of Aminosteril N administration is described in Example 4 of the present application. In particular, Example 4 describes the administration of a 2030 mL infusion of Aminosteril N to 26 patients in 1 to 5 therapeutic doses. Eleven out of 26 patients (42%) experienced one or more episodes of vomiting, which calculated to up to 30 episodes of severe vomiting per treatment. In one of the eleven patients, the vomiting was so severe that infusion of Aminosteril N was discontinued and replaced with 50 grams of L-lysine (see page 16, lines 3-12). Hence, one would expect that administration of the amino acid cocktail Synthamin 14

disclosed in Hammond would result in even more serious adverse side-effects than that which Applicants found to occur after Aminosteril N administration.

In conclusion, Applicants submit that neither the '059 patent, the '894 patent, or Hammond, alone or in combination, teaches or suggests the new and unexpected findings of the method and therapeutic composition of the claimed invention, namely, that the administration to a patient of a combination of two specific amino acids, e.g., lysine and arginine, which together show a surprising synergistic effect when combined. Thus lower doses of the two claimed amino acids are needed, which avoids serious side effects and inhibits renal uptake of protein and peptides which may be damaging to the kidneys. In other words, the dual low dose administration of lysine (or a derivative) and one of anginine or ornithine (or a derivative), and the unexpected results achievable thereby, are not taught by any or all of the prior art.

For all of the foregoing reasons, amended claims 53 and 58 are in condition for allowance. Reconsideration of the rejections and allowance of all pending claims 53, 55-58 and 60-63 are respectfully requested.

Respectfully submitted,

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